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# Contrast-Induced Nephropathy and Prophylactic Administration of Sodium Bicarbonate with Coronary Angiography

## **Abstract**

**Background:** Coronary angiography is associated with a 4-15% chance of contrast-induced nephropathy (CIN). While the cause of CIN is still not understood, renal ischemia and free radical effects on tubular epithelial cells are thought to be responsible. In addition to increased hydration, the antioxidant properties of sodium bicarbonate are thought to decrease the direct toxic effects seen in CIN. The question of this treatment's efficacy has been asked since its inception, and no definitive conclusion has been reached. The purpose of this systematic review is to compare and contrast the most current randomized trials, assessing the quality of the studies involved, and to give a practicing clinician a more complete understanding of the outcomes.

**Methods:** Exhaustive search of available medical literature from 2006 to the present for randomized control trials regarding contrast-induced nephropathy in patients undergoing non-emergent coronary angiography. The reviewed studies examined the significance of sodium bicarbonate in addition to hydration versus hydration alone, measured by pre- and post-operative renal function.

**Results:** The five studies reviewed do not agree on the efficacy of sodium bicarbonate administration for renal prophylaxis, although all state that increased hydration is the gold standard, and that sodium bicarbonate is not associated with increased adverse effects. Multiple studies showed no statistical significance of renal protection when compared to hydration alone, although methods of administration and several other confounders were identified when the trials were analyzed en masse.

**Conclusion:** Repeated, definitive, single protocol studies have yet to determine the efficacy of sodium bicarbonate administration in patients undergoing cardiac angiography, but all current studies can agree that use of this compound for renal prophylaxis is not associated with an increased risk to the patient.

## **Degree Type**

Capstone Project

## **Degree Name**

Master of Science in Physician Assistant Studies

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**Keywords**

Coronary angiography, nephropathy, catheterization, sodium bicarbonate

**Subject Categories**

Medicine and Health Sciences

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**Contrast-Induced Nephropathy and Prophylactic  
Administration of Sodium Bicarbonate with Coronary Angiography**

Jacob S Weidert, PA-S



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 14<sup>th</sup>, 2010

Faculty Advisor: Mary Von

Clinical Graduate Project Coordinators:

Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD

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## **Biography**

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Jacob S Weidert is a native of Washington State. He is a graduate of the University of Wyoming where he majored in Health Sciences, was a two-time captain of the UW swim team, and a competitor during the 2000 USA Swimming Olympic Trials. After receiving his undergraduate degree in 2004, he returned to his beloved state of Washington, where he began working in interventional cardiology. After receiving his graduate degree, Jacob looks forward to pursuing a career in either rural family medicine or continuing his work in cardiology. It is with great pleasure and relief that he submits this paper in satisfaction of the requirements of his Masters of Science Degree in Physician Assistant Studies.

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## Abstract

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**Background:** Coronary angiography is associated with a 4-15% chance of contrast-induced nephropathy (CIN). While the cause of CIN is still not understood, renal ischemia and free radical effects on tubular epithelial cells are thought to be responsible. In addition to increased hydration, the antioxidant properties of sodium bicarbonate are thought to decrease the direct toxic effects seen in CIN. The question of this treatment's efficacy has been asked since its inception, and no definitive conclusion has been reached. The purpose of this systematic review is to compare and contrast the most current randomized trials, assessing the quality of the studies involved, and to give a practicing clinician a more complete understanding of the outcomes.

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**Conclusion:** Repeated, definitive, single protocol studies have yet to determine the efficacy of sodium bicarbonate administration in patients undergoing cardiac angiography, but all current studies can agree that use of this compound for renal prophylaxis is not associated with an increased risk to the patient.

**Keywords:** Coronary angiography, nephropathy, catheterization, sodium bicarbonate



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To *my parents*: Thank you for the time, the sleep, the worry, and the good ole' fashioned guilt you gave to teach me to help myself. You held me to a higher standard, and now I hold myself to that same benchmark.

To *my brother and sisters*: For being there with a kind, sarcastic wit to brighten my day. For always having a guest bed available on my many travels, and the early morning/late night trips to the airport.

To *my PA school family*: By learning with you, I learned through you. The time we spent together will forever be a part of my fondest memories.

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Table 1: Jadad Validity Scoring

Table 2: Summary Matrix of Literature

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## List of Abbreviations

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ARF.....	Acute Renal Failure
CHF.....	Congestive Heart Failure
CI.....	Confidence Interval
CIN.....	Contrast-induced Nephropathy
CKD.....	Chronic Kidney Disease
GFR.....	Glomerular Filtration Rate
D5W.....	Dextrose 5% in Water
NAC.....	N-Acetylcysteine
NS.....	Normal Saline
PCI.....	Percutaneous Intervention/Angioplasty/Stenting
RCT.....	Randomized Controlled Trial

# **Contrast-Induced Nephropathy and Prophylactic Administration of Sodium Bicarbonate with Coronary Angiography**

## **BACKGROUND**

Patients undergoing elective coronary angiography are at risk of several complications, one of the most common of which is contrast-induced nephropathy (CIN).<sup>1</sup> However, administration of contrast media is imperative for imaging during coronary angiographies and percutaneous interventions. Incidence of CIN occurrence can vary between 2% in low-risk populations to more than 50% in high risk patients,<sup>2</sup> with up to 15% in patients identified with mild renal impairment.<sup>1</sup> CIN is associated with several adverse outcomes, the most noteworthy of which are an increased need for hemodialysis, persistent decline in renal function, and increased mortality.<sup>1,2</sup> Contrast-induced nephropathy is also strongly associated with an extended inpatient care period, and increased costs of care.<sup>3,4</sup> In hospitalized patients, CIN has become the third-leading cause of acute renal failure (ARF) affecting 12% of individuals. This is second only to hypotension and post-surgical complications.<sup>4,5</sup> In those patients needing hospital care after acquiring CIN, the mortality rate is 34%.<sup>6</sup> Several factors increase a patient's risk of CIN, including but not limited to chronic kidney disease (CKD), volume and type of contrast media used, and pre-existing patient conditions.<sup>5</sup> Diabetes, male gender, congestive heart failure (CHF), increased age, anemia, and a decreased circulating blood volume are just some of the conditions that increase a patient's risk of CIN.<sup>3,4,7,8</sup>

The mechanism of renal damage from contrast-induced nephropathy is not well understood. The most commonly accepted theories focus on renal ischemia and tubular

epithelial cell toxicity.<sup>9,10</sup> Renal ischemia is thought to be a consequence of the vasoconstrictive effects of the hyperosmolar renal blood flow during contrast administration, while the free radical nature of the contrast media in the renal tubule is thought to be responsible for the tubular epithelial cell toxicity.<sup>10</sup>

Several strategies have been proposed to provide renal protection during angiographic procedures. Plasma-expanding fluids (ie, mannitol), diuretics, dopamine and hemofiltration have all been evaluated with limited results.<sup>11-20</sup> The use of N-acetylcysteine (NAC) has shown some promise, but considerable heterogeneity in study parameters and outcomes reflect conflicting conclusions on NAC's effectiveness.<sup>10</sup> Volume expansion in the peri-procedural period remains the only undisputed modality to have shown any statistical promise concerning CIN.<sup>21</sup>

Sodium bicarbonate is often used as a means of preventing CIN, based on sodium bicarbonate's antioxidant properties and alkalinizing abilities in the renal tubule.<sup>12</sup> Bicarbonate reacts and neutralizes peroxynitrite, a species of reactive oxygen created by nitric oxide in the renal tubule,<sup>22</sup> and it is also thought to inhibit the Harber-Weiss reaction. This reaction creates a superoxide from a hydrogen peroxide ion and free oxygen, and is activated in acidic environments.<sup>23</sup> By increasing the pH of the renal tubule, this reaction is disrupted, therefore decreasing cytotoxic damage to the epithelial cells in the kidney.

This systematic review was performed to evaluate the potential and practical effects of sodium bicarbonate administration compared to normal hydration, as it pertains to preventing contrast-induced nephropathy. To accomplish this, the most pertinent and current randomized research trials have been gathered to compare, contrast, and evaluate

the protocols, outcomes, interpretations, and validity of those studies in a comprehensive manner. Due to its ease of administration in angiographic procedures, its low cost, and its apparent lack of adverse effects, sodium bicarbonate could potentially be a standard of treatment in all patients undergoing coronary imaging with renal insufficiency.

## **METHODS**

### **Search Protocol**

This systematic review analyzed the most current research that enriches our understanding of CIN and the use of sodium bicarbonate to prevent it. Therefore, only studies published in the last 4 years contrasting sodium bicarbonate treatment with normal hydration were included. Only studies of prospective, randomized trials were included in this review, although cohort and case controlled studies were referenced for background and ancillary information.

An exhaustive literature search was conducted using the comprehensive search engines Medline, CINAHL, and ISI Web of Science. The following terms were used: coronary angiography, nephropathy, sodium bicarbonate, and contrast-induced nephropathy. Results of this search were compared, collated, and cross-referenced, checking for duplications of studies and critical outcomes. The reference sections of relevant articles were reviewed for pertinent information associated with the subject matter. All articles in the systematic review were then critically appraised and ranked using a standard Jadad score for validity (Table 1).

## **Inclusions/Exclusions**

Inclusion criteria limited the search to English language publications of non-emergent coronary procedures on adult human subjects using sodium bicarbonate as the primary intervention. Exclusion criteria were any randomized controlled trials published before 2006, and those studies comparing interventions other than sodium bicarbonate with normal hydration.

## **RESULTS**

Results of the online search illuminated seventy-five possible journal articles for evaluation using the search terms included, on the three databases. After eliminating duplications and irrelevant sources (letters, opinion articles, etc), the inclusion/exclusion criteria were applied to fourteen sources. A final number of five prospective, randomized, controlled trials were evaluated for this systematic review. A summary of their pertinent information can be found in Table 2.

### **Vasheghani-Farahani et al**

Taking place in Tehran, Iran at the Tehran Heart Center, Vasheghani-Farahani et al<sup>24</sup> conducted a single center study which was composed of 265 patients, randomized into two experimental arms in a double-blind fashion, who were undergoing elective coronary angiography. All participants had a stable serum creatinine of 1.5mg/dl or greater within two weeks of the procedure, which is indicative of decreased renal function. Parameters between the two groups were similar, with a mean age of 63.3 years, and a population consisting of 83% males. Patients were enrolled in either the saline arm, receiving 1075ml of 0.9% normal saline, or the bicarbonate arm which

received 75ml of 8.4% bicarbonate mixed with 1000ml of normal saline. Administration was equal in both arms, with an initial bolus of 3ml/kg for 1 hour, then decreasing to 1ml/kg/hr for 6 hours after the procedure. Fluid volume was limited at 110kg, and all diuretics were withheld on the day of the procedure. Three formulations of contrast agent were used, Iohexol, a non-ionic, low-osmolar agent was used in 254 patients. Iohexol plus amidotrizoic acid, a non-ionic, high-osmolar agent was used in 8 patients, and Iodixanol a non-ionic, iso-osmolar agent was utilized in 2 patients. The volumes of contrast media used in the two groups were 113.2ml and 115.0ml. Serum creatinine was assessed prior to the procedure, as well as at days 2 and 5 after the procedure. Urine pH was measured prior to angiography, and at the first spontaneous voiding after. Primary endpoint of the study was the development of CIN, measured as an absolute or relative increase in the serum creatinine by 0.5mg/dl or 25%, respectively. Secondary outcomes were at least a 25% decrease in the baseline GFR within 48 hours, duration of hospital stay, and urine pH after the initial bolus of contrast.<sup>24</sup>

Of the 265 participants, 40 were excluded from the final analysis due to variance from the study protocol, with 3 patients receiving increased hydration, 1 patient was enrolled with a GFR<20ml/min, and 36 patients with that were determined to have unstable creatinine levels based on the measurements just prior to the procedure. These 36 participants were included in the preliminary analysis based on the intent-to-treat principle. The final analysis revealed no statistically significant differences between the two groups, even when the 36 patients were included. Within the saline arm, 7 of the patients (5.9%) satisfied the primary endpoint, while 9 patients (7.4%) in the bicarbonate



arm were diagnosed with primary endpoint CIN ( $p=0.6$ ). Serum creatinine levels at day 5, and secondary endpoints did not significantly differ ( $p=0.6$ ,  $p=0.3$ ).<sup>24</sup>

### **Adolph et al**

Adolph et al,<sup>25</sup> a single-center, prospective, randomized, controlled trial in Rostock, Germany involved 148 subjects undergoing elective angiography or PCI with stable renal insufficiency. Renal insufficiency was defined as two serum creatinine measurements greater than 1.2mg/dl (but with no more than a 5% difference the two), within a 12 week period prior to the procedure. Subjects were randomized in a double-blinded fashion into two groups. The saline group consisted of 72 patients who received 154mEq of sodium chloride in 846ml of D5W, while the bicarbonate group was made up of 76 patients who received 154mEq of sodium bicarbonate in 846ml of D5W. Participants did not statistically differ in demographic, clinical, or biochemical characteristics, with a mean age of 70.1 in the bicarbonate group, and 72.7 in the saline group ( $p=0.543$ ). Of the total participants, 77.9% were male ( $n=113$ ). Fluids were administered at rates of 2ml/kg/hr for 2 hours prior to the procedure, and this was decreased to 1ml/kg/hr during and for 6 hours after the procedure. Diuretics were withheld the day of the procedure. Non-ionic, iso-osmolar Iodixanol was used in all patients, with mean volumes of 141ml in the bicarbonate group, and 138ml in the saline group ( $p=0.532$ ). Serum creatinine, cystatin C, plasma viscosity, and urinary enzymes were recorded prior to the procedure to establish a baseline, and again at days 1 and 2. The primary endpoint was defined as an increase in serum creatinine of  $\geq 0.5$ mg/dl or 25% above baseline within days the first 48 hours after the procedure. Significant

changes in cystatin C, plasma viscosity, or urinary enzymes were considered secondary endpoints.<sup>25</sup>

In this particular study, only 145 patients had a complete follow-up. Two patients were lost due to emergencies arising from coronary artery bypass grafting and pulmonary edema. Another patient refused follow-up after not completing the study. Final analysis revealed no statistical significance in the primary endpoint. The sodium bicarbonate group had 3 patients (4.2%), and the saline group had 2 patients (2.7%) that were diagnosed with CIN ( $p=0.614$ ). There were no significant differences in the secondary endpoints. Hospital stays were increased in patients diagnosed with CIN, but all 5 patients returned to baseline serum creatinine levels within 14 days of the procedure.<sup>25</sup>

### **Mauro et al**

Mauro et al<sup>21</sup> performed a prospective, randomized trial, consisting of 502 patients (mean age 74, 41% female) undergoing planned coronary angiography with or without PCI, was performed in a single-blinded fashion at a single center in Prato, Italy. All patients included in the trial had estimated creatinine clearances of  $<60\text{ml/min}$ . Of the 502 subjects, 252 were assigned to a standard hydration therapy of 0.9% normal saline, given at  $1\text{ml/kg/hr}$  for 12 hours before and after the procedure. The remaining participants were assigned to the sodium bicarbonate group, and received a mixture of sodium bicarbonate and 5% dextrose with water at  $154\text{mEq/l}$ , respectively. This solution was administered at  $3\text{ml/kg}$  for 1 hour before the procedure, and at  $1\text{ml/kg/hr}$  for 6 hours after. All patients received oral NAC twice daily from the day prior to the procedure until the day after the procedure. Fluid restrictions were placed on patients classified

with left ventricular heart failure. Iodixanol contrast media, a nonionic, iso-osmolar agent, was used in all cases, with an average contrast volume used of 170ml in the saline group, and 160ml used in the bicarbonate group. Serum creatinine levels were measured at admission, and routinely on days 1-5 and on day 10 in the post-procedural timeline. An additional assessment was taken at 1 month on individuals who were diagnosed with CIN to establish persistent renal impairment. The primary endpoint of the study was an increase of 0.5mg/dl, which the study defined as CIN, within five days after the procedure. Secondary endpoints included an increase  $\geq 25\%$  in the baseline serum creatinine, in-hospital death, acute pulmonary edema, and a need for either dialysis or hemofiltration.<sup>21</sup>

In total, 54(10.8%) patients in the study developed CIN, as defined by the primary endpoint, 29 (11.5%) in the saline group, and 25 (10.0%) in the bicarbonate group ( $p=0.60$ ). No statistical difference was noted in secondary endpoints, with even distribution of adverse events across both arms of the study ( $p=0.13$ ).<sup>21</sup>

### **Brar et al**

The study authorized by Brar et al,<sup>9</sup> looked at patients undergoing elective coronary angiography with or without PCI, at a single center in Los Angeles, all with moderate to severe CKD as defined by a glomerular filtration rate of 60mL/min or less, and at least one of the following: age over 75 years, diabetes mellitus, hypertension, or congestive heart failure. Patients in this prospective trial were randomly sorted into a single-blind study consisting of 353 subjects. Populations were similar in respect to comorbidities, with a mean age of 71, and a total of 36.2% female participants. Participants

were randomly sorted into two arms, a saline group consisting of 178 participants receiving 0.9% normal saline, and a bicarbonate group with 175 participants receiving 150mEq of sodium bicarbonate in 1L of 5% dextrose with water. Infusion rates were equal in the two groups, at 3ml/kg for 1 hour prior to the procedure, and decreased to 1.5ml/kg during the procedure and for 4 hours following it. Hydration levels were limited to those needed in a 100kg individual. Ioxilan, a non-ionic, low-osmolar contrast media was used in all participants, with an average administration of 137ml in the saline group, and 126ml in the bicarbonate group. Procedural duration was also noted in this study, but differences were not statistically significant between the two groups( $p=0.08$ ). Serum creatinine levels were measured as patients were admitted to the treatment center, and subjects were asked to have them drawn again on days 1 and 2 following the angiography. All serum creatinine levels were followed until they either returned to baseline, or established a new baseline with impaired kidney function. The primary endpoint of the study was the development of CIN, defined in this study as a 25% decrease in the GFR from the baseline using the lowest recorded rate measured post-procedurally. Secondary endpoints included an increase of  $\geq 25\%$  in the serum creatinine, dialysis within 30 days after the procedure, or any/all cause mortality. Those participants who developed CIN were asked to return for another GFR within a 2 to 8 week period to establish whether renal impairment persisted.<sup>9</sup>

In total, 323 of the original 353 were included in the primary CIN analysis. Thirty patients were lost to follow-up because they either did not undergo the angiography ( $n=3$ ), or they did not have proper GFR data 1-4 days after the procedure ( $n=27$ ). At the end of the primary analysis, 45 (13.9%) patients in the study developed

CIN, as defined by the primary endpoint. The saline group had 24 (14.6%) patients who met the primary endpoint, while the bicarbonate group had 21 (13.3%) patients ( $p=0.82$ ). Secondary endpoints were not statistically significant between the two groups, with the recording of adverse events extended to 6 months. These measurements included the thirty individuals from the study that were lost to follow up, based on the intent-to-treat principle.<sup>9</sup>

### **Tamura et al**

Tamura et al,<sup>26</sup> a prospective, controlled, single-blinded trial, took place at two hospitals in Oita, Japan. In total, 144 patients undergoing elective angiography or PCI, with a measured serum creatinine of 1.1mg/dl or greater, were randomized to receive either standard hydration with normal saline, or standard hydration with a single bolus of sodium bicarbonate (20ml) five minutes prior to contrast exposure. A total of 72 individuals were assigned to each group. Characteristics relating to clinical, procedural, and biochemical parameters were not statistically different. Men made up 87.5% of the population ( $n=126$ ), with a mean age of 72.8 years for all subjects. Participants in both groups were administered 0.9% normal saline at 1ml/kg/hr for 12 hours before and after the procedure. Fluids were limited to 80ml/hr in all patients, and were decreased by half in individuals suffering from CHF with an ejection fraction <40%. Diuretics were withheld the day of the procedure. Non-ionic, low-osmolar Iohexol was used in all patients. Contrast volume was an average of 82.1ml in the bicarbonate group, and 87.8ml in the normal hydration group. Serum creatinine levels were measured prior to the procedure, and daily for 3 days afterward. Additional creatinine measurements were

taken in all individuals who had a decrease in renal function after the procedure. All creatinine levels were taken using an enzyme method that differs from the technique used in many Western countries, resulting in a decreased measurement by an average of 0.2mg/dl. Arterial gas and urine pH measurements were also taken before and after the procedure. The definition of the primary endpoint was an increase from the baseline serum creatinine of  $\geq 25\%$  or 0.5mg/dl, defined as CIN, within 3 days after the procedure. Secondary endpoints were percentage changes of serum creatinine from the baseline, and adverse clinical events within one week of the procedure, including pulmonary edema, renal failure requiring dialysis or hemofiltration, or death.<sup>26</sup>

All subjects finished the trial with complete follow-up. All 144 participants were included in the final analysis. There was statistical difference in the two experimental arms, with 1 patient (1.4%) in the bicarbonate arm, and 9 patients (12.5%) in the normal hydration arm meeting the primary endpoint criteria for CIN ( $p=0.017$ ). Satisfaction of secondary endpoints showed percentage changes of creatinine that were significantly different ( $p<0.001$ ), with insufficient statistical variance of adverse events, with only 1 patient in the normal hydration arm needing dialysis ( $p=0.99$ ). Measurements of urinary pH and arterial blood gases showed significant differences when compared to the normal hydration group ( $p<0.001$ ).<sup>26</sup>

## **DISCUSSION**

### **Validity**

In this analysis, all studies chosen for systematic review were randomized, controlled trials of high quality with good samples sizes. They relied on similar exclusion criteria with similar populations from around the globe, including Iran, Germany, Japan, Italy, and the US. Jadad Validity scoring was used to evaluate the potential strength of each trial's outcomes (Table 1). Each article was given a validity score, with possible rankings from 0-5. Two trials, Vasheghani-Farahani et al<sup>24</sup> and Adolph et al,<sup>25</sup> both scored the highest possible with 5 points apiece, while all other studies scored a 3 on the Jadad scale. In those studies<sup>9,21,26</sup> that scored a 3, all failed to score a 5 because they stated they were single-blinded, or did not mention if they were single or double blinded.

### **Outcomes**

In reviewing the results, the majority of evidence suggests that there is limited, if any, benefit from the use of sodium bicarbonate over normal hydration alone concerning contrast-induced nephropathy. All of the studies agreed that the standard therapy of hydration decreased the occurrence of CIN, but only Tamura et al<sup>26</sup> showed statistical reductions in the incidence of CIN when patients were administered sodium bicarbonate over normal hydration alone. These results are somewhat confusing, especially considering the administration of sodium bicarbonate for coronary angiography procedures, and angiographic imaging in general, is a very commonplace procedure.

Considering the mechanisms by which CIN is thought to occur, either by renal ischemia or free radical toxicity, the evidence shows that ischemia may play the larger role. Urinary pH was measured in only 2 studies,<sup>24,26</sup> but both studies saw a marked rise in the urinary pH that was expected in the sodium bicarbonate groups. The increased pH demonstrates that while sodium bicarbonate was available for free radical scavenging in the kidney, the total effect may not be as large as thought before. This is consistent with the utilization of increased hydration for prevention of CIN, as the increased fluid accessible to the glomerular complex may offset the ischemia that would otherwise damage the nephron.

There was no significant divergence between the two therapies concerning adverse events in any of the studies. Complications of pulmonary edema, dialysis, hemofiltration, and all cause mortality were not statistically noteworthy when the two treatments of sodium bicarbonate and normal hydration were contrasted.

### **Limitations of Study**

**Endpoint variance**— Of the presented studies, one major difference seen between them was defining CIN, both in serial testing and duration. For instance, Mauro et al<sup>21</sup> defined CIN as an increase of >0.5mg/dl in the serum creatinine within two days. Two studies<sup>24,25</sup> defined CIN as either an increase in the serum creatinine of >0.5mg/dl or a relative increase of 25%, within 2 days. Another study<sup>26</sup> defined CIN in the same way, but within 3 days. Brar et al,<sup>9</sup> did not define CIN using serum creatinine at all, but instead used estimated GFR levels. The authors of this trial acknowledged that evaluating acute renal changes with GFR is not as well established as the use of serum



creatinine. The literature notes that the development of CIN peaks at post-procedural days 3-5, however while some of the present studies monitored renal function during these days, they were not the primary outcome. Possible reasons for the lack of follow-up on days 3-5 may be problems with subject compliance and reliability outside the hospital setting, although this is not expressly stated. Resumption of diuretics, asthma medications, and other environmental factors were also not monitored once the patient was discharged from the hospital in any of the studies.

Another note should also be made that Tamura et al<sup>26</sup> used a different method to measure the serum creatinine than the common Jaffe method used in Western countries, resulting in a serum creatinine that is 0.2mg/dl lower on average. This method was used in all participants, and its effect on the study is unknown.

**Protocol-** In the current review, one major confounder were the protocols utilized to administer both the interventions and comparison controls in the studies. For instance, infusion rates varied from study to study, with pre-procedural rates ranging from 1ml/kg/hr x 12 hours to 3ml/kg/hr x 1 hour. In one study, Mauro et al,<sup>21</sup> the infusion rates varied between the two experimental arms, with the bicarbonate group receiving much less hydration both pre-procedurally and post procedurally. The amount of sodium bicarbonate utilized in each study was different, as was the volume of contrast media injected into the patient, although it is unknown if these differences are of statistical significance when compared across the different trials.

Another disparity revealed in this review was the solution employed to deliver the sodium bicarbonate. While an optimal study would have compared normal saline vs. normal saline with sodium bicarbonate as an intervention, as in 3 of the trials; both Brar

et al<sup>9</sup> and Mauro et al<sup>21</sup> compared normal saline to sodium bicarbonate mixed with D5W. The use of this crystalloid solution allows for differences in hydration, as some volume of the free water is lost into the interstitial space after the glucose has been metabolized, whereas a greater amount of the saline solution remains in the intravascular space to be available for the glomerular complex to filter.

Lastly, the given studies used different types of contrast media for visualization during angiography. All were non-ionic, but variations in the osmolarity of the different media result in fluctuations in the CIN effect size. Iso-osmolar contrast has been proven to have a lower incidence of CIN, when compared to low-osmolar contrast (6.1%-15.4% incidence).<sup>27</sup> Two studies,<sup>21,25</sup> used iso-osmolar agents, two studies<sup>9,26</sup> used low-osmolar agents, and Vasheghani-Farahani et al<sup>24</sup> used all three levels of osmolarity, ranging from low to iso to high, although 96% of their patients were administered the low-osmolar agent Iohexol. While this may not change the results of an individual study, when applied to a systematic review of several studies, the implications show that differing protocols across all studies make a larger perspective analysis difficult.

## **CONCLUSIONS**

While there exists strong research showing that sodium bicarbonate is not effective in the treatment of contrast-induced nephropathy; variations in dosage, administration, hydration protocol, and outcomes confound the evidence. Throughout all studies, no statistically significant evidence showed sodium bicarbonate to be deleterious to the patient's health, or increase the risk of adverse events. The wise clinician will use this evidence to augment treatment at their own discretion, evaluating a patient's renal

status, pre-existing risk factors, and potentially harmful outcomes if sodium bicarbonate is employed or not.

Future avenues of study should focus on resolving a universal definition and method of measurement for contrast induced nephropathy. It is important that these studies use equivalent protocols for both experimental groups, leaving only the administration of sodium bicarbonate as a variable. While all of the studies were single-center in nature, a broad multicenter study using the above recommendations could help future clinicians decide to use sodium bicarbonate in their practice, or conclude that this treatment is an antiquated prophylactic treatment without statistically reliable results. Either way, this treatment is a low-cost, non-harmful, and easily administered therapy that almost any patient can be treated with.

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## **TABLES**

**TABLE 1:   Jadad Validity Scoring**

<b>VALIDITY PROTOCOL</b>	<b>SCORE</b>
Was the trial/study randomized?	<b>1</b>
Was the method of randomization appropriate for the study, and was it described?	<b>1</b>
Was the study double-blinded?	<b>1</b>
Was the method of blinding the study appropriate and described?	<b>1</b>
Were dropouts/withdrawals for the study accounted for?	<b>1</b>
Deduction for inappropriate randomization.	<b>Subtract (-1)</b>
Deduction for inappropriate double blinding.	<b>Subtract (-1)</b>

**TABLE 2: Summary Matrix of Literature**

<b>Author</b>	<b>Study Size &amp; Type</b>	<b>Population</b>	<b>Intervention &amp; Comparison</b>	<b>Outcomes</b>	<b>Jadad Score</b>
Vasheghani-Farahani et al <sup>24</sup> (10/2009)	N=265 RCT	Patients with stable renal disease, defined as a serum creatinine >1.5mg/dl	Sodium Bicarbonate with Normal Saline vs. Normal saline	Serum creatinine increase of >0.5mg/dl or >25% from baseline within 2 days	5
Adolph et al <sup>25</sup> (9/2008)	N=145 RCT	Patients with stable renal disease defined as 2 serum creatinine levels >1.2mg/dl	Sodium Bicarbonate with D5W vs. Sodium Chloride with D5W	Serum creatinine increase of >0.5mg/dl or >25% from baseline within 2 days	5
Mauro et al <sup>21</sup> (8/2009)	N=502 RCT	Patients with stable renal disease defined as a GFR <60ml/min	Sodium Bicarbonate with D5W vs. Normal Saline	Serum Creatinine increase of >0.5mg/dl within 2 days	3
Brar et al <sup>9</sup> (9/2009)	N=353 RCT	Patients with stable renal disease defined as a GFR <60ml/min and 1 defined comorbidity.	Sodium Bicarbonate with D5W vs. Normal Saline	GFR decrease of >25% within 4 days	3
Tamura et al <sup>26</sup> (10/2009)	N=144 RCT	Coronary angiography in patients with baseline creatinine of 1.1mg/dl	Sodium Bicarbonate bolus with Normal Saline vs. Normal Saline	Serum creatinine increase of >0.5mg/dl or 25% from baseline within 3 days	3